ORIGINAL ARTICLE

Noradrenergic and Serotonergic Function in Posttraumatic Stress Disorder

Steven M. Southwick, MD; John H. Krystal, MD; J. Douglas Bremner, MD; C. A. Morgan III, MD; Andreas L. Nicolaou, PhD; Linda M. Nagy, MD; David R. Johnson, PhD; George R. Heninger, MD; Dennis S. Charney, MD

Background: Yohimbine hydrochloride produces marked behavioral and cardiovascular effects in combat veterans with posttraumatic stress disorder (PTSD). In the present study, yohimbine was used as a probe of noradrenergic activity, and meta-chlorophenylpiperazine (m-CPP) as a probe of serotonergic activity. To our knowledge, this is the first study to describe the behavioral and cardiovascular effects of meta-CPP in patients with PTSD, and to compare these effects with those of yohimbine.

Method: Twenty-six patients with PTSD and 14 healthy subjects each received an intravenous infusion of yohimbine hydrochloride (0.4 mg/kg), m-CPP (1.0 mg/kg), or saline solution on 3 separate test days in a randomized balanced order and in double-blind fashion. Behavioral and cardiovascular measurements were determined at multiple times.

Results: Eleven (42%) of the patients with PTSD experienced yohimbine-induced panic attacks and had significantly greater increases compared with controls in anxiety, panic, and PTSD symptoms, but not in cardiovascular measurements. Eight patients (31%) with PTSD experienced m-CPP–induced panic attacks and had significantly greater increases compared with controls in anxiety, panic, and PTSD symptoms, and in standing diastolic blood pressure. Yohimbine-induced panic attacks tended to occur in different patients from m-CPP–induced panic attacks.

Conclusion: These data suggest the presence of 2 neurobiological subgroups of patients with PTSD, one with a sensitized noradrenergic system, and the other with a sensitized serotonergic system.

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From the Clinical Neurosciences Division, National Center for Post-Traumatic Stress Disorder, Veterans Affairs Medical Center, West Haven, Conn (Drs Southwick, Krystal, Bremner, Morgan, Nicolaou, Nagy, Johnson, Heninger, and Charney); and the Department of Psychiatry, Yale University School of Medicine, New Haven, Conn (Drs Southwick, Krystal, Bremner, Morgan, Nagy, Johnson, Heninger, and Charney).

THE NORADRENERGIC system has been the most intensively studied neural system in humans suffering from posttraumatic stress disorder (PTSD). This system was chosen as a focus of study because of extensive preclinical data linking it to fear and anxiety,[1-9] vigilance,[10-12] selective attention,[12-15] and consolidation of memory.[16-24] Persons with PTSD often suffer with analogous symptoms of hypervigilance, anxiety, fear, and recurrent intrusive memories. Norepinephrine also was selected because of its central role in the sympathetic nervous system and in what is commonly termed the "flight or fight response." Since 1918, many psychophysiological studies consistently have shown heightened sympathetic nervous system reactivity in combat veterans with trauma-related symptoms.[25-33]

Evidence of noradrenergic dysregulation in PTSD also has come from investigations of neuroendocrine and peripheral catecholamine receptor systems. Twenty-four–hour urine norepinephrine excretion[34,35] has been reported as significantly elevated and platelet α_2-adrenergic receptor number[36] and lymphocyte basal cyclic adenosine monophosphate and adenylate cyclase levels[37] as significantly decreased in combat veterans with PTSD compared with normal controls. In a study that simultaneously evaluated psychophysiological and peripheral noradrenergic activity in response to viewing a combat film, Blanchard et al[38] reported a parallel rise in blood pressure, heart rate, subjective distress, and plasma norepinephrine in combat veterans with PTSD.

We recently reported on the use of yohimbine hydrochloride as a probe of peripheral and central noradrenergic reactivity in 20 combat veterans with PTSD.[39] Yohimbine is an α_2-adrenergic receptor antagonist that activates noradrenergic neurons by blocking the presynaptic α_2-adrenergic autoreceptor.[40-42] Patients with PTSD had potentiated biochemical, behavioral, and cardiovascular responses to yohimbine. Indeed, 70% of patients expe-

PATIENTS AND METHODS

PATIENTS

Twenty-six male patients were recruited from a 4-month inpatient PTSD treatment program at the National Center for Post-Traumatic Stress Disorder located in the Connecticut Department of Veterans Affairs Medical Center, West Haven, Conn. Military records, including the DD214, were used to verify Vietnam combat experience. Exclusion criteria included organic mental disorders; neurologic disorders, such as seizures; cardiovascular disease, including hypertension, history of myocardial infarction, or significant electrocardiographic abnormalities; and serious medical illnesses, such as diabetes and chronic hepatitis.

Mean±SEM age was 41.8±0.5 years. Mean±SEM weight was 85.6±2.6 kg. A 4-week drug-free period, monitored by staff, was required of all patients before the first test session.

Each patient who gave voluntary written informed consent for participation in this study met criteria for PTSD using the structured clinical interview for *DSM-III-R*[92] and had a Mississippi Post-Traumatic Stress Disorder scale score greater than 107.[93] Mean±SEM severity of PTSD on the Mississippi scale was 132.9±3.8 of a possible 175. This is considered to be severe PTSD.[93]

A consensus diagnostic team finalized all diagnoses. Six patients and 15 patients met current *DSM-III-R* criteria for panic disorder and major depression, respectively, on admission to the study. Eighteen patients met lifetime *DSM-III-R* diagnostic criteria for major depression, 6 for lifetime panic disorder, and 20 for lifetime alcohol dependence.

HEALTHY SUBJECTS

Fourteen healthy male subjects, recruited from responses to advertisements, gave voluntary written informed consent for participation in the study and were determined to be free of mental disorder based on the results of a structured psychiatric interview. None reported a history of mental illness in first-degree relatives or use of psychoactive medication for at least 4 weeks. Mean±SEM age was 39.8±3.7 years. Mean±SEM weight was 81.0±2.7 kg.

None had a history of serious medical illness. All had normal results on physical examination, electrocardiogram, and laboratory tests of renal, hepatic, pancreatic, hematopoietic, and thyroid function. Healthy controls and patients were paid for participation in this study.

PROCEDURES

On 3 separate test days during 20-minute infusions in a randomized balanced order and in double-blind fashion, patients and healthy subjects received an intravenous infusion of yohimbine hydrochloride (0.4 mg/kg), m-CPP (0.1 mg/kg), or saline solution. On each test day, subjects received two 10-minute infusions. On the saline test day, both infusions consisted of 0.9% saline solution. On the m-CPP test day, both 10-minute infusions contained 0.05 mg/kg of m-CPP for a total of 0.1 mg/kg for 20 minutes. On the test day for yohimbine, one infusion contained yohimbine hydrochloride (0.4 mg/kg administered for 10 minutes), and the other infusion consisted of saline solution infused for 10 minutes. The m-CPP doses and rates of infusion were identical to those of previously reported studies in healthy subjects,[88] and in patients with panic disorder,[77] obsessive-compulsive disorder,[83] and schizophrenia.[90] Investigators and raters were not aware of the medication status except for the research pharmacist. The interval between infusions was generally 4 to 7 days.

Subjects arrived on the Neurobiological Studies Unit by 8:30 AM. They fasted overnight for 10 hours, were supine with their heads elevated during most of the 5-hour

rienced panic attacks and 40% experienced flashbacks after yohimbine administration. The 70% panic attack rate closely resembles the experience reported in patients with panic disorder,[43-45] raising the possibility that PTSD and panic disorder share a common neurobiological abnormality related to the noradrenergic system.[39]

Although yohimbine clearly has pronounced effects in combat veterans with PTSD, it is unclear whether other anxiogenic probes that alter the function of different neurotransmitter systems would produce similar reactions in this patient population. The present study was designed to test the specificity of the yohimbine response in combat veterans with PTSD and to evaluate potential serotonergic (5-HT) contributions to trauma-related symptoms. Altered 5-HT activity following severe stress or trauma has been reported in animal and human studies.[46-53] In humans, for example, platelet 5-HT uptake has been reported as significantly decreased in patients with PTSD compared with normal controls,[53] and specific 5-HT reuptake inhibitors have been found to be moderately efficacious in treating the full range of PTSD-specific symptoms in a subgroup of traumatized patients.[54-58] Furthermore, low 5-HT activity in humans has been associated with aggression,[59] impulsivity,[59] and suicide,[60] behaviors that often are reported in combat veterans with PTSD.

In the present study, yohimbine was used as a probe of noradrenergic activity, and meta-chlorophenylpiperazine (m-CPP) was used as a probe of 5-HT activity in combat veterans with PTSD compared with normal controls. The m-CPP interacts with the 5-HT transporter[61] and several 5-HT receptor subtypes, including, in descending affinity, the 5-HT_3, 5-HT_{2C}, $5\text{-HT}_{2A/B}$, 5-HT_7, 5-HT_{1A}, and 5-HT_{1D} receptors.[62-66] Meta-chlorophenylpiperazine is a partial agonist at 5-HT_1 receptors,[65-67] a partial agonist or antagonist of the 5-HT_2 receptor,[68-70] and an antagonist of 5-HT_3 receptors.[71,72] Relative to its potency at 5-HT_{2C} receptors, m-CPP seems to possess markedly lower affinities for α_1, α_2, dopamine$_1$, and dopamine$_2$ receptors.[63,73] Meta-chlorophenylpiperazine has been used widely to investigate 5-HT function in neuropsychiatric disorders such as panic disorder,[74-77] obsessive-compulsive disorder,[78-83] schizophrenia,[84] depression,[85-87] and alcoholism.[88-91] These investigations disclose that, depending on the disorder under study,[74-91] m-CPP has a broad spectrum of behavioral

test day, and stood only to use the bathroom and to permit recordings of their standing blood pressure and pulse rate. Sleep was not permitted. Blood pressure and pulse rate were measured in the usual clinical fashion at 15 and 0.5 minutes before and at 40, 60, 120, and 180 minutes following the dose.

Self-report behavioral ratings were administered 15 minutes before and at 20, 60, 120, and 180 minutes after infusion. Panic attack symptoms were assessed using a 27-item Panic Attack Symptom Scale (PASS) that includes the 13 *DSM-III-R* panic symptoms. Possible scores range from 27 to 108. Symptoms are rated on a 4-point scale (1=not present to 4=severe). The PTSD-specific symptoms were measured using a scale consisting of 8 *DSM-III-R* items (anger, difficulty concentrating, distant from others, emotionally numb, flashbacks, hypervigilance, intrusive thoughts, and startle). Symptoms are rated on a 5-point scale (1=not present to 5=worst ever), with possible scores ranging from 8 to 40.

To determine whether a panic attack or flashback had occurred during test sessions, all subjects were evaluated by a research psychiatrist (S.M.S. or J.H.K.) and a research nurse who were not aware of the medication status. This evaluation was based on direct clinical observation and patient self-report.

Panic attacks were determined using the following criteria: (1) increase in severity of 4 or more *DSM-III-R* panic attack symptoms on the PASS compared with baseline; (2) crescendo increase in severe subjective anxiety of at least 25 mm from baseline on a 100-mm visual analog scale for anxiety; (3) for patients with a history of panic attacks, the drug-induced anxiety state had to be similar to a naturally occurring panic attack in intensity and specific symptoms; (4) consensual agreement of the 2 research psychiatrists (S.M.S. and J.H.K.) that a panic attack had occurred based on the aforementioned 3 criteria and nursing notes.

Flashbacks were determined using the following criteria: (1) reexperiencing a past traumatic event during the course of drug or placebo infusion; (2) involvement of 1 or more sensory modalities (hearing, seeing, smelling, and/or feeling); (3) for patients with a history of flashbacks, the drug-induced reexperiencing state must have been similar to a naturally occurring flashback; and (4) consensual agreement of the 2 research psychiatrists that a flashback had occurred.

DATA ANALYSIS

Data were analyzed with standard Statistical Analysis System procedures. Effects of yohimbine and m-CPP on anxiety, PTSD symptom ratings, and cardiovascular variables were evaluated with repeated-measures analysis of variance (ANOVA). Initial analyses included all time points. Subsequent pairwise comparisons involved baseline and peak measurements between particular test days for individual items. Assessments of statistical significance included main effects of diagnosis, drug (placebo vs yohimbine or m-CPP), and time. The α levels were adjusted for multiple comparisons.

We used *t* tests to determine how and when patients differed from healthy subjects in response to both active agents compared with placebo and with each other. Baseline values were subtracted from values at each time point for the variable of interest, resulting in a change score for each time point. Subtracting this change score for placebo from that of yohimbine resulted in an estimate of the net yohimbine effect. Similar estimates were calculated comparing m-CPP with placebo and m-CPP with yohimbine.

Pearson correlation coefficients (for symptoms significantly increased in response to either or both active agents compared with placebo) evaluate the relations between peak changes from baseline in individual symptoms following m-CPP and yohimbine. The α levels were adjusted for multiple comparisons.

effects, including exacerbation of anxiety, psychosis, and obsessions.

In the present report, 26 combat veterans with *DSM-III-R* PTSD and 14 noncombat healthy controls were administered intravenous yohimbine, m-CPP, and placebo on 3 separate test days. Subjects were rated for panic attacks, flashbacks, anxiety symptoms and *DSM-III-R* PTSD-specific symptoms, and blood pressure and heart rate responses. To our knowledge, this is the first study to describe the subjective, behavioral, and cardiovascular effects of m-CPP in patients with PTSD and the first to compare these effects with those of yohimbine.

RESULTS

FREQUENCY OF PANIC ATTACKS AND FLASHBACKS

Yohimbine produced panic attacks in 11 (42%) of 26 patients and 1 (7%) of 14 controls. Eight patients (31%) and no controls had a panic attack in response to m-CPP. Three patients had panic attacks in response to both active compounds. No panic attacks occurred after placebo administration. Flashbacks occurred after yohimbine in 8 patients (31%) and no controls. In response to m-CPP, 7 patients (27%) and no controls had flashbacks. Four of these patients had flashbacks while receiving both drugs. Two patients had flashbacks during placebo administration, both of whom also had flashbacks while receiving yohimbine and 1 while taking m-CPP. The drug administered on the first day was neither more nor less likely to cause a panic attack or a flashback than the drug administered on the second day.

PANIC ATTACK SYMPTOM SCALE

Effects of Yohimbine

Change Over Time From Baseline (**Figure 1**). Total PASS score was significantly higher following yohimbine compared with placebo in patients with PTSD ($F=14.84$, $df=4,100$, $P<.001$; at 20 minutes—$t=5.96$, $df=25$, $P<.001$; at 60 minutes—$t=3.04$, $df=25$, $P<.01$) and in healthy controls ($F=18.62$, $df=4,52$, $P<.001$; at 20 minutes—$t=5.54$, $df=13$, $P<.001$; at 60 minutes—$t=3.64$, $df=13$,

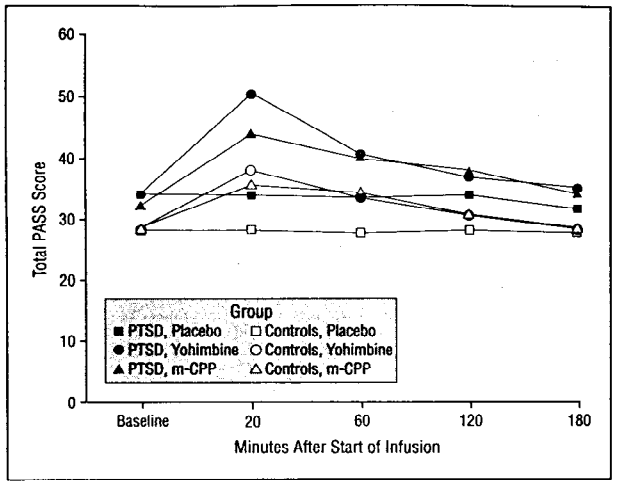

Figure 1. *Effects of yohimbine hydrochloride, meta-chlorophenylpiperazine (m-CPP), and placebo on total Panic Attack Symptom Scale (PASS) score in healthy controls and patients with posttraumatic stress disorder (PTSD).*

$P<.005$). The increased effects of yohimbine over placebo, however, were not significantly different in patients compared with controls ($F=1.35$, $df=4,152$, $P=.56$).

Peak Change From Baseline (**Table 1**). Patients and healthy controls were not significantly different on the total PASS score or on any of the individual items. However, patients who had yohimbine-induced panic attacks had significantly greater increases on the total PASS score compared with healthy controls and on 2 individual items: fear of going crazy and goose bumps. Compared with patients without yohimbine-induced panic attacks, patients with PTSD and panic attacks had significantly greater increases on the total PASS score, fear of losing control, fear of going crazy, and muscle twitching.

Effects of m-CPP

Change Over Time From Baseline (Figure 1). Total PASS score was significantly higher following m-CPP compared with placebo in patients ($F=7.56$, $df=4,100$, $P<.001$; at 20 minutes—$t=4.13$, $df=25$, $P<.005$; at 60 minutes—$t=3.21$, $df=25$, $P<.005$; at 120 minutes—$t=2.96$, $df=25$, $P<.01$; at 180 minutes—$t=2.82$, $df=25$, $P<.01$) and in healthy controls ($F=9.10$, $df=4,52$, $P<.001$; at 20 minutes—$t=3.17$, $df=13$, $P<.01$; at 60 minutes—$t=2.98$, $df=13$, $P<.02$), but not in patients compared with controls.

Peak Change From Baseline (Table 1). Change in total PASS score or in any of the individual items did not differ significantly between the total group of patients and controls. Patients with m-CPP–induced panic attacks had significantly greater increases on the total PASS score and on the items of choking or smothering sensation and feelings of unreality and irritability than did controls. Patients who experienced m-CPP–induced panic attacks, compared with patients who did not, had significantly greater increases on the total PASS score and on the following individual symptoms: choking or smothering sensation, feelings of unreality, muscle twitching, tremor or shakiness, uncoordination, and weakness.

Comparison of Yohimbine and m-CPP Behavioral Effects on PASS

In the group of 26 patients with PTSD, 11 individual PASS symptoms changed significantly over time in response to yohimbine or m-CPP. Responses to yohimbine were as follows ($df=1,25$ for all): sweating—$F=27.12$, $P<.001$; muscle aches—$F=13.79$, $P<.001$; nausea—$F=9.35$, $P<.01$; light-headedness—$F=25.92$, $P<.001$; dizziness—$F=13.19$, $P<.002$; restlessness—$F=8.93$, $P<.01$; hot or cold flashes—$F=16.78$, $P<.001$; uncoordination—$F=4.89$, $P<.05$; goose bumps—$F=32.69$, $P<.001$; tremor or shakiness—$F=27.12$, $P<.001$; and runny nose—$F=18.65$, $P<.001$. Responses to m-CPP were as follows ($df=1,25$ for all): sweating—$F=4.38$, $P<.05$; muscle aches—$F=15.24$, $P<.001$; nausea—$F=14.25$, $P<.001$; light-headedness—$F=12.48$, $P<.01$; dizziness—$F=15.52$, $P<.001$; restlessness—$F=14.60$, $P<.001$; hot or cold flashes—$F=11.41$, $P<.01$; uncoordination—$F=15.72$, $P<.001$; goose bumps—$F=5.74$, $P<.05$; tremor or shakiness—$F=7.66$, $P<.01$; and runny nose—$F=4.38$, $P<.05$. After adjusting for multiple comparisons ($\alpha=.004$), Pearson correlations between peak changes over time were not significant for any of the symptoms.

PTSD SCALE

Effects of Yohimbine

Change Over Time From Baseline (**Figure 2**). Total PTSD score was significantly higher following yohimbine compared with placebo in patients ($F=8.60$, $df=4,100$, $P<.001$; at 20 minutes—$t=4.09$, $df=25$, $P<.005$; at 60 minutes—$t=3.00$, $df=25$, $P<.01$) and in healthy controls ($F=6.83$, $df=4,52$, $P<.003$; at 20 minutes—$t=3.17$, $df=13$, $P<.01$; at 60 minutes—$t=2.31$, $df=13$, $P<.04$). Patients with PTSD had a significantly greater yohimbine-placebo increase than did controls overall ($F=2.68$, $df=4,152$, $P<.04$) and at 20 minutes ($t=-3.00$, $df=29.3$, $P<.01$).

Peak Change From Baseline (**Table 2**). Peak change in total PTSD score and in individual items did not differ significantly between patients and controls. Patients with yohimbine-induced panic attacks had significantly greater increases in total PTSD score and intrusive thoughts than controls. On the other hand, there were no significant differences between patients with and without yohimbine-induced panic attacks.

Effects of m-CPP

Change Over Time From Baseline (Figure 2). Total PTSD score was significantly higher following m-CPP compared with placebo in patients with PTSD ($F=4.61$, $df=4,100$, $P<.002$; at 20 minutes—$t=2.86$, $df=25$, $P<.01$, at 60 minutes, $t=3.27$, $df=25$, $P<.005$; at 120 minutes—$t=3.14$, $df=25$, $P<.005$; at 180 minutes—$t=2.47$, $df=25$, $P<.03$) and in healthy controls ($F=8.13$, $df=4,52$, $P<.001$; at 20 minutes—$t=3.28$, $df=13$, $P<.01$; at 60 minutes—$t=2.67$, $df=13$, $P<.02$), but not in patients compared with healthy controls ($F=1.31$, $df=4,152$, $P=.27$).

Peak Change From Baseline (Table 2). There were no significant differences in any individual symptom or

Table 1. Effects of Intravenous Yohimbine or Meta-chlorophenylpiperazine Compared With Placebo on the Panic Attack Symptom Scale*

	Patients With Posttraumatic Stress Disorder†					
	With Panic Attacks		Without Panic Attacks		Healthy Subjects (n=14)	
Symptom	Baseline	Peak Change	Baseline	Peak Change	Baseline	Peak Change
Yohimbine hydrochloride vs placebo						
Fear of losing control						
Placebo	1.64 (0.30)	0.18 (0.14)	1.30 (0.14)	0.50 (0.23)‡	1.00 (0.00)	0.07 (0.07)
Yohimbine	1.68 (0.30)	1.41 (0.40)	1.50 (0.18)	−0.10 (0.11)	1.00 (0.00)	0.14 (0.10)
Fear of going crazy						
Placebo	1.50 (0.25)	−0.05 (0.08)	1.17 (0.09)	0.23 (0.17)‡	1.00 (0.00)	0.00 (0.00)§
Yohimbine	1.45 (0.24)	1.18 (0.35)	1.27 (0.15)	0.13 (0.10)	1.00 (0.00)	0.00 (0.00)
Goose bumps						
Placebo	1.09 (0.09)	0.00 (0.13)	1.17 (0.19)	0.03 (0.08)	1.00 (0.00)	0.00 (0.00)§
Yohimbine	1.09 (0.09)	1.55 (0.34)	1.03 (0.03)	1.03 (0.28)	1.00 (0.00)	0.21 (0.15)
Muscle twitching						
Placebo	1.18 (0.18)	0.18 (0.18)	1.20 (0.08)	0.47 (0.17)‡	1.07 (0.07)	0.00 (0.00)
Yohimbine	1.27 (0.19)	2.00 (0.36)	1.27 (0.17)	0.67 (0.24)	1.18 (0.14)	0.82 (0.29)
Total PASS score						
Placebo	33.45 (2.82)	3.00 (2.63)	34.20 (2.02)	2.73 (1.77)‡	27.79 (0.23)	0.71 (0.37)§
Yohimbine	34.05 (3.19)	28.05 (3.29)	33.97 (1.70)	11.10 (2.66)	28.54 (0.51)	9.89 (1.68)
m-CPP vs placebo						
Choking or smothering sensation						
Placebo	1.13 (0.13)	0.00 (0.00)	1.06 (0.06)	0.00 (0.00)‡	1.00 (0.00)	0.07 (0.07)§
m-CPP	1.06 (0.06)	1.44 (0.37)	1.06 (0.06)	0.22 (0.13)	1.00 (0.00)	0.14 (0.10)
Feelings of unreality						
Placebo	1.56 (0.26)	−0.19 (0.13)	1.17 (0.08)	0.33 (0.18)‡	1.00 (0.00)	0.07 (0.07)§
m-CPP	1.13 (0.13)	2.00 (0.38)	1.22 (0.10)	0.33 (0.16)	1.00 (0.00)	0.36 (0.17)
Irritability						
Placebo	1.69 (0.25)	0.06 (0.24)	1.50 (0.17)	0.17 (0.19)	1.04 (0.04)	−0.04 (0.04)§
m-CPP	1.75 (0.30)	1.50 (0.28)	1.33 (0.13)	0.44 (0.16)	1.00 (0.00)	0.07 (0.07)
Muscle twitching						
Placebo	1.25 (0.13)	0.25 (0.13)	1.17 (0.11)	0.39 (0.17)‡	1.07 (0.07)	0.00 (0.00)
m-CPP	1.13 (0.13)	1.63 (0.38)	1.06 (0.06)	0.28 (0.14)	1.21 (0.21)	0.43 (0.25)
Tremor, shakiness						
Placebo	1.25 (0.16)	0.00 (0.00)	1.14 (0.07)	0.36 (0.16)‡	1.00 (0.00)	0.00 (0.00)
m-CPP	1.13 (0.08)	1.75 (0.35)	1.08 (0.06)	0.47 (0.16)	1.00 (0.00)	0.71 (0.27)
Uncoordination						
Placebo	1.31 (0.21)	0.06 (0.06)	1.14 (0.10)	0.08 (0.14)‡	1.00 (0.00)	0.00 (0.00)
m-CPP	1.06 (0.06)	1.44 (0.26)	1.14 (0.10)	0.36 (0.15)	1.00 (0.00)	0.36 (0.17)
Weakness						
Placebo	1.50 (0.21)	0.00 (0.16)	1.14 (0.08)	0.19 (0.16)‡	1.07 (0.05)	0.00 (0.09)
m-CPP	1.38 (0.25)	1.63 (0.36)	1.11 (0.09)	0.33 (0.11)	1.00 (0.00)	0.57 (0.17)
Total PASS score						
Placebo	35.81 (3.39)	2.44 (2.31)	33.03 (1.84)	3.03 (1.92)‡	27.79 (0.23)	0.71 (0.37)§
m-CPP	33.56 (2.62)	32.06 (4.13)	31.39 (1.41)	9.00 (1.73)	28.25 (0.39)	7.89 (2.11)

*Values are given as mean (±SEM). m-CPP indicates meta-chlorophenylpiperazine; PASS, Panic Attack Symptom Scale.

†Patients with posttraumatic stress disorder and yohimbine-induced panic attacks, n=11; without yohimbine-induced panic attacks, n=15; with m-CPP–induced panic attacks, n=8; without m-CPP–induced panic attacks, n=18.

‡Statistically significant ($P<.002$) group×drug×time interaction (patients with panic attacks vs patients without panic attacks).

§Statistically significant ($P<.002$) group×drug×time interaction (patients with panic attacks vs healthy controls).

in total PTSD score between the patient group as a whole and controls. Compared with controls, patients who had m-CPP–induced panic attacks had a significantly greater increase in total PTSD score and in the following PTSD symptoms: anger, distant from others, flashbacks, hypervigilance, intrusive thoughts, and startle. Compared with patients without m-CPP–induced panic attacks, those with panic attacks had a significantly greater increase in total PTSD score and in the following specific symptoms: anger, difficulty concentrating, distant from others, and hypervigilance.

Comparison of Yohimbine and m-CPP Behavioral Effects on PTSD Scale

Relative to placebo, 4 symptoms (distant from others, intrusive thoughts, emotionally numb, and flashbacks) increased significantly in response to m-CPP or yohimbine in the group of 26 patients with PTSD. Responses to yohimbine were as follows (df=1,25 for all): distant from others, $F=6.48$, $P<.05$; intrusive thoughts, $F=4.28$, $P<.05$; emotionally numb, $F=19.12$, $P<.001$; and flashbacks, $F=9.67$, $P<.01$. Responses to m-CPP were as fol-

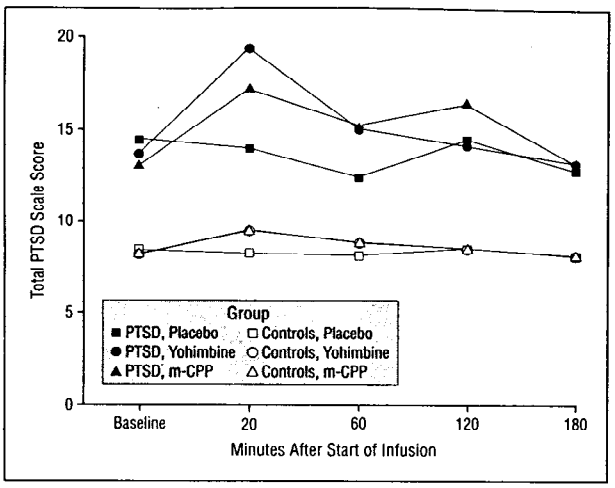

Figure 2. *Effects of yohimbine hydrochloride, meta-chlorophenylpiperazine (m-CPP), and placebo on total Post-Traumatic Stress Disorder (PTSD) scale score in healthy controls and patients with PTSD.*

lows (df=1,25 for all): distant from others, F=13.33, P<.01; intrusive thoughts, F=10.47, P<.01; emotionally numb, F=19.67, P<.001; and flashbacks, F=5.43, P<.05. Following adjustments for multiple comparisons (α=.013), the Pearson correlation between peak change over time for yohimbine and m-CPP was significant only for the symptom of distant from others (r=.49, df=24, P<.01).

BLOOD PRESSURE AND HEART RATE PEAK CHANGE FROM BASELINE

Effects of Yohimbine

Patients with PTSD did not differ significantly from healthy controls in changes in blood pressure and heart rate over time. Furthermore, no significant differences were observed in any blood pressure and heart rate measurements when comparing patients who had yohimbine-induced panic attacks with patients who did not have yohimbine-induced panic attacks and when comparing patients who had yohimbine-induced panic attacks with healthy controls.

Effects of m-CPP

When comparing the entire patient group with healthy controls, no significant differences were observed in measurement changes of blood pressure and heart rate over time. Similarly, there were no significant differences when comparing patients who had m-CPP–induced panic attacks with patients who did not have m-CPP–induced panic attacks, nor when comparing patients who had m-CPP–induced panic attacks with healthy controls.

COMMENT

Similar to previously published findings in combat veterans with PTSD, yohimbine infusion caused increases in anxiety, panic, and PTSD-specific symptoms. Although the incidence of yohimbine-induced panic attacks in patients with PTSD (42%) was lower than the 70% observed by Southwick et al[39] and the 60% by Bremner et al,[94] the rate was considerably higher than that found in the present control group (7%). Furthermore, the rate of yohimbine-induced flashbacks was similar among patients with PTSD in all 3 studies (31%, 40%, and 30%, respectively).

The subgroup of patients with yohimbine-induced panic attacks had significantly greater increases in total PASS and total PTSD scale scores than did healthy controls. These data suggest that a subgroup of patients with PTSD, and not the entire group, has a potentiated anxiogenic and PTSD symptom behavioral response to yohimbine. Because the primary action of yohimbine is on the noradrenergic system, these findings suggest that a subgroup of combat veterans with PTSD has increased reactivity of this system.[40-42,95,96]

Although the effect of yohimbine on blood pressure was greater in patients than controls, the difference was not significant. This contrasts with the observations in our earlier study.[39] This discrepancy potentially may be explained by differences in the 2 patient populations. In the first study, not all patients were elective admissions and therefore likely to be more acutely ill.

The present data indicate that m-CPP also causes increases in anxiety, panic, and PTSD-specific symptoms among combat veterans with PTSD. Meta-chlorophenylpiperazine induced panic attacks in 31% and flashbacks in 27% of patients. Because we believe this is the first report of m-CPP challenge in patients with PTSD, it is impossible to compare the present findings with earlier work. However, our findings concur with clinical data supporting a relation between 5-HT function and impulsivity,[59] aggression,[59] and suicide,[60] clinical features commonly associated with PTSD.

Like the subgroup of patients with yohimbine-induced panic attacks, the group with m-CPP–induced panic attacks also had significantly greater increases in total PASS and total PTSD scale scores compared with healthy controls. Thus, some but not all patients with PTSD have potentiated responses to m-CPP, with rapid increases in both panic and PTSD-specific symptoms. These data are consistent with preclinical studies showing that chronic stress results in increased behavioral responses to m-CPP[46-52] that seem to be mediated by 5-HT_{2C} receptors.[68-70] Thus, the current findings suggest that some patients with PTSD may have supersensitive 5-HT_{2C} receptors.

Yohimbine-induced panic attacks and m-CPP–induced panic attacks tended to occur in different patients. Only 3 (19%) of 16 patients with drug-induced panic attacks had the attacks on both active test days. The remaining 13 patients (81%) had their panic attacks following administration of yohimbine or m-CPP, but not both, suggesting the possibility of at least 2 biological subtypes of PTSD, one characterized by dysregulated noradrenergic and the other by dysregulated 5-HT function. These data indicate that panic attack and flashback induction in combat veterans with PTSD is not specific to yohimbine or m-CPP and suggest that these phenomena do not represent a specific response to α_2-adrenergic receptor blockade or 5-HT_{2C}–receptor stimu-

Table 2. Effects of Intravenous Yohimbine or Meta-chlorophenylpiperazine Compared With Placebo on the Posttraumatic Stress Disorder Scale*

	Patients With PTSD†					
	With Panic Attacks		Without Panic Attacks		Healthy Subjects (n=14)	
Symptom	Baseline	Peak Change	Baseline	Peak Change	Baseline	Peak Change
Yohimbine hydrochloride vs placebo						
Intrusive thoughts						
Placebo	1.64 (0.20)	0.27 (0.30)	1.87 (0.29)	0.33 (0.27)	1.07 (0.07)	−0.07 (0.07)§
Yohimbine	1.73 (0.22)	1.55 (0.33)	1.53 (0.20)	0.53 (0.26)	1.00 (0.00)	0.00 (0.00)
Total PTSD score						
Placebo	13.82 (1.57)	1.09 (1.53)	14.77 (1.55)	1.17 (0.87)	8.46 (0.22)	0.04 (0.22)§
Yohimbine	14.45 (1.60)	10.18 (1.82)	13.03 (1.21)	3.97 (1.49)	8.32 (0.19)	1.39 (0.41)
m-CPP vs placebo						
Anger						
Placebo	1.88 (0.39)	−0.13 (0.08)	1.83 (0.28)	0.50 (0.24)‡	1.00 (0.00)	0.00 (0.00)§
m-CPP	1.38 (0.21)	2.13 (0.57)	1.67 (0.22)	0.22 (0.13)	1.00 (0.00)	0.00 (0.00)
Difficulty concentrating						
Placebo	2.63 (0.42)	−0.13 (0.23)	2.00 (0.19)	0.39 (0.18)‡	1.18 (0.11)	−0.11 (0.06)
m-CPP	2.31 (0.33)	1.81 (0.41)	2.14 (0.15)	0.42 (0.23)	1.07 (0.05)	0.71 (0.21)
Distant from others						
Placebo	2.00 (0.41)	−0.13 (0.21)	1.94 (0.25)	0.33 (0.15)‡	1.07 (0.07)	−0.07 (0.07)§
m-CPP	1.88 (0.41)	1.88 (0.41)	1.78 (0.25)	0.72 (0.18)	1.00 (0.00)	0.14 (0.10)
Flashbacks						
Placebo	1.50 (0.37)	0.00 (0.16)	1.17 (0.12)	0.11 (0.21)	1.00 (0.00)	0.00 (0.00)§
m-CPP	1.31 (0.25)	1.19 (0.46)	1.03 (0.03)	0.42 (0.22)	1.00 (0.00)	0.00 (0.00)
Hypervigilance						
Placebo	1.69 (0.25)	0.31 (0.34)	1.83 (0.21)	0.39 (0.18)‡	1.14 (0.11)	−0.07 (0.05)§
m-CPP	1.56 (0.32)	1.81 (0.44)	1.75 (0.18)	0.42 (0.16)	1.07 (0.07)	0.00 (0.00)
Intrusive thoughts						
Placebo	1.88 (0.36)	0.13 (0.21)	1.72 (0.22)	0.39 (0.27)	1.07 (0.07)	0.07 (0.07)§
m-CPP	1.69 (0.25)	1.69 (0.47)	1.44 (0.18)	0.83 (0.21)	1.04 (0.03)	−0.04 (0.03)
Startle						
Placebo	1.56 (0.31)	0.94 (0.29)	1.19 (0.12)	1.19 (0.29)	1.00 (0.00)	0.29 (0.16)§
m-CPP	1.50 (0.31)	1.88 (0.39)	1.06 (0.06)	1.00 (0.27)	1.00 (0.00)	0.07 (0.07)
Total PTSD score						
Placebo	15.31 (2.31)	0.19 (1.45)	13.94 (1.24)	1.56 (0.97)‡	8.46 (0.22)	0.04 (0.22)§
m-CPP	13.50 (1.99)	11.59 (2.55)	12.83 (1.02)	3.72 (1.11)	8.18 (0.10)	1.32 (0.48)

*Values are given as mean (±SEM). PTSD indicates posttraumatic stress disorder; m-CPP, meta-chlorophenylpiperazine.
†No. of patients in each group given in footnote to Table 1.
‡Statistically significant ($P<.006$) group×drug×time interaction (patients with panic attacks vs patients without panic attacks).
§Statistically significant ($P<.006$) group×drug×time interaction (patients with panic attacks vs healthy controls).

lation. Instead, it seems that panic attacks and flashbacks can be induced in this population by multiple anxiogenic agents that have differing mechanisms of action. For example, Rainey et al[97] reported panic attacks and flashbacks in combat veterans after infusion of sodium lactate.

While yohimbine and m-CPP have marked effects on anxiety and PTSD-specific symptoms relative to placebo, there was little correlation between the behavioral responses to yohimbine and m-CPP in individual patients. Four PTSD-specific symptoms increased significantly relative to placebo in response to yohimbine and/or m-CPP in the entire patient group. After correction for multiple comparisons, in only 1 of the 4 symptoms was the peak change following yohimbine significantly correlated with the peak change following m-CPP. Similarly, none of the 11 PASS symptoms that changed significantly in response to yohimbine or m-CPP had peak changes following yohimbine that significantly correlated with peak changes following m-CPP. This suggests that m-CPP and yohimbine have distinct effects on anxiety and PTSD symptoms in individual patients with PTSD and further supports the concept of specific neurobiological subtypes in this disorder.

The possibility of neurobiological subtypes and differential behavioral responses to m-CPP and yohimbine has potential clinical relevance. To date, no one therapy consistently has been shown to be effective for the treatment of PTSD.[98-100]

From the results of the present study, it is possible to speculate that patients with increased behavioral sensitivity to yohimbine might benefit from drugs that reduce noradrenergic function, such as clonidine hydrochloride or propranolol hydrochloride, and might experience an initial exacerbation of symptoms if treated with noradrenergic reuptake inhibitors such as desipramine hydrochloride. Patients with increased behavioral sensitivity to m-CPP might respond preferentially to drugs with primary actions on 5-HT function. The behavioral effects of m-CPP have been shown to be reduced by chronic fluoxetine hydrochloride and clomipramine hydrochloride treatment in patients with obsessive-

compulsive disorder.[80] The matching of biological subtypes with appropriate pharmacological agents may increase the efficacy of pharmacotherapy in the treatment of PTSD.

Intrusive memories and flashbacks were induced by yohimbine and m-CPP. These memories often were remarkably vivid and palpable. Identification of neurotransmitters and neuropeptides involved in memory encoding and retrieval has been the subject of considerable preclinical investigation. The tendency for yohimbine to elicit traumatic memory recall and flashbacks may relate to β-adrenergic–receptor stimulation in the amygdala and cortical structures.[16,17,24] Less is known about mechanisms by which m-CPP might effect traumatic memories and flashbacks, although other 5-HT agonists, such as lysergic acid diethylamide (LSD) are capable of inducing flashbacks[101-103] that seem to be mediated by the 5-HT_{2A} receptor. It may be that the induction of flashbacks by m-CPP and LSD share a common mechanism involving this 5-HT receptor.

There are a number of potential limitations in the present study. First, although yohimbine and m-CPP have been used as probes of noradrenergic and 5-HT function, respectively, both agents have effects on multiple neurotransmitter systems. For example, yohimbine binds to 5-HT receptors and m-CPP to adrenergic receptors.[73,95,96,104] However, m-CPP clearly has greater affinity than yohimbine for 5-HT receptors, and yohimbine has greater affinity than m-CPP for adrenergic receptors.[73,104]

Second, patients in this study were treatment-seeking veterans with chronic and pervasive trauma-related symptoms. They are not necessarily representative of the veteran population as a whole. It is unclear if the present results can be generalized to non–treatment-seeking combat veterans (with and without PTSD), civilians with noncombat PTSD, and persons who have been more recently traumatized.

Third, because our patients with PTSD had a high rate of comorbid panic disorder, major depression, and alcoholism, it could be argued that these comorbid disorders rather than PTSD accounted for the observed results. This is an especially important issue for panic disorder, because yohimbine and m-CPP are known to cause panic attacks in patients with panic disorder[43-45,74-77] but not in patients with major depressive disorder[105] or alcoholism.[88-91] In the present study, however, 8 of 11 patients with yohimbine-induced panic attacks and 6 of 8 with m-CPP–induced panic attacks did not meet comorbid criteria for panic disorder, making it unlikely that panic disorder alone can explain these findings. Similarly, because 4 of 11 and 7 of 11 patients with yohimbine-induced panic attacks, and 3 of 8 and 7 of 8 with m-CPP–induced panic attacks did not meet comorbid criteria for current major depression and current alcohol abuse, respectively, each of these 2 comorbid diagnoses alone cannot explain the above findings. Nevertheless, the influence of comorbid Axis I diagnoses on the behavioral effects of the 2 study agents cannot be definitively determined because of the small sample size.

Along with preclinical observations that stress profoundly alters the function of many neurotransmitter and neuropeptide systems, the aforementioned behavioral responses to yohimbine and m-CPP support the view of PTSD as a multisystem neurobiological disorder. There is now ample clinical evidence showing chronic alterations in the noradrenergic, 5-HT, and glucocorticoid systems in many traumatized persons even 25 years after exposure to traumatic stressors.[106] With the elucidation of biological subtypes, it is hoped that specific treatments can be developed and targeted toward underlying neurobiological disturbances, with the ultimate goal of reducing the level of suffering in persons who have been severely traumatized.

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Reprints: Steven M. Southwick, MD, National Center for Post-Traumatic Stress Disorder, Veterans Affairs Medical Center, Department of Psychiatry (116A), West Haven, CT 06516.

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